INTELLECTUAL
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सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

1804/843

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**352/Del/2003** dated **21st March 2003.***

Witness my hand this 28th day of May 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

C07D211/00

0352-03

21 MAR 2003

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1. We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 , Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF PIPERIDYLMETHYL-INDANONES"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR
b. MOHAN PRASAD
c. ASOK NATH
d. NITIN MAHESHWARI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

ORIGINAL

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), India.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10
Fax No. (91-124) 2342027

6. Following declaration was given by the inventors in the convention country:

We, YATENDRA KUMAR, MOHAN PRASAD, ASOK NATH, NITIN MAHESHWARI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (YATENDRA KUMAR)

b. (MOHAN PRASAD)

c. (ASOK NATH)

d. (NITIN MAHESHWARI)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **686513** dated :**20.12.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **21ST** day of **March, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR PREPARATION OF PIPERIDYLMETHYL-INDANONES

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Processes for the preparation of piperidylmethyl-indanones, which are useful intermediates for the preparation of benzyl-piperidylmethyl-indanones, are provided. Further, processes for the preparation of benzyl-piperidylmethyl-indanones, which are active compounds for the treatment of CNS disorders, are provided.

Benzyl-piperidylmethyl-indanones such as donepezil have an excellent pharmacological action as prophylactic or medicament for senile dementia, especially for Alzheimer. Several processes have been reported for the preparation of benzyl-piperidylmethyl-indanones such as in US 4895841, US 5606064, US 6252081, US 6413986, WO 97/22584 and J. Med.Chem. 1995, 38 (24), 4821-4829. The processes require multiple steps or complicated purification processes such as chromatography and therefore inevitably lead to poorer yields or purity.

In one aspect, a process for preparing a 2-(4-piperidinyl) methyl-1-indanone of formula II, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are identical or different, and represent hydrogen, straight or branched -chain alkyl, alkoxy, alkoxycarbonyl, alkyl- or dialkyl-aminocarbonyloxy, trifluoromethyl, or halogen, is provided, comprising reducing a 2-(4-pyridyl) methyl-1-indanone of the formula III, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above.

In a further aspect, a process for preparing the 2-(4-pyridyl) methyl-1-indanone of formula III, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above, is provided comprising selectively reducing 2-(4-pyridyl) methylene-1-indanone of formula IV, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above.

Formation of a complex mixture of impurities is minimized or eliminated altogether by avoiding direct reduction of the compound of formula IV to the compound of formula II.

The 2-(4-piperidinyl) methyl-1-indanone of formula II, wherein R^1, R^2, R^3, and R^4 are as defined above, or a salt thereof, obtained from the reduction of compound of formula III above may be reacted with a benzyl derivative of formula V, wherein X is a leaving group, in the presence of a base to obtain a benzyl-piperidylmethyl-indanones of formula I, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above.

Compound of formula I may thus be obtained in good yield and purity without resorting to chromatographic purification.

In yet another aspect, an improved process for preparing a benzyl-piperidylmethyl-indanones of formula I, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are identical or different, and represent hydrogen, straight or branched -chain alkyl, alkoxy, alkoxycarbonyl, alkyl- or dialkyl-aminocarbonyloxy, trifluoromethyl, or halogen, is provided, comprising reacting a 2-(4-piperidinyl) methyl-1-indanone of formula II, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above, with a benzyl derivative of formula V, wherein X is a leaving group, in the presence of an inorganic base and a phase transfer catalyst.

The benzylation rection is faster in the presence of phase transfer catalyst and side products are minimized. Compound of formula I may thus be obtained in good yield and purity without resorting to chromatographic purification.

Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, and tert-butyl. Examples of alkoxy groups include methoxy, ethoxy, isopropoxy, and tert-butoxy. The term "halogen" refers to a member of the family fluorine, chlorine, bromine, or iodine. Examples of alkoxylcarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, and tert-butoxycarbonyl. Examples of alkyl- or dialkyl-aminocarbonyloxy include methylaminocarbonyloxy, and dimethylaminocarbonyloxy. In

a particular example R^1 and R^4 represent hydrogen and R^2 and R^3 represent methoxy in the compounds of formula I, II, III and IV.

The reduction of the compound of formula III to compound of formula II may be achieved by hydrogenation in the presence of a catalyst. The hydrogenation catalyst used for the reduction are the customary hydrogenation catalysts known in organic chemistry, such as transistion metal compounds. Examples of transistion metal compounds include platinum compound such as platinum oxide, ruthenium compound such as ruthenium oxide and rhodium compounds such as rhodium/carbon.

The hydrogenation may be carried out at normal pressure, or at elevated pressure depending on the choice of catalyst. In general, it may be carried out at a hydrogen pressure range from 1 to 10 atmospheres, or at a hydrogen pressure range from 1 to 2 atmospheres.

The hydrogenation temperature is not critical and may be varied depending on the choice of catalyst and/or pressure employed. For example the hydrogenation may be carried out at a temperature range from –20°C to 120°C, or at a temperature range from 0°C to 80°C. In one particular example it may be carried out at a temperature range from 10°C to 35°C.

Compounds of formula III can be produced by methods known in the art such as the procedures disclosed in US 6252081or obtained by the selective reduction of compounds of formula IV.

The reduction of the compound of formula IV to compound of formula II may be achieved by selective hydrogenation in the presence of a catalyst or by other conventional procedures for carbon- carbon double bond reduction, which do not reduce the pyridine ring of the compound of formula IV.

The catalyst used for the selective hydrogenation are the customary hydrogenation catalysts known in organic chemistry, such as transistion metal compounds, used under milder conditions. Examples of suitable transistion metal compounds include platinum compound such as platinum/carbon, palladium compound such as palladium/carbon, palladium hydroxide, and nickel compound such as Raney nickel.

The selective hydrogenation may be carried out at normal pressure, or at somewhat elevated pressure depending on the choice of catalyst. In general, it may be carried out at a hydrogen pressure range from 1 to 5 atmospheres, or at a hydrogen pressure range from 1 to 2 atmospheres.

The hydrogenation temperature may be varied depending on the choice of catalyst and/or pressure employed. For example the hydrogenation may be carried out at a temperature range from –20°C to 60°C, or at a temperature range from 0°C to 40°C. In one particular example it may be carried out at a temperature range from 10°C to 35°C.

Conventional procedures for selective carbon- carbon double bond reduction, which may be employed include using hydrazine hydrate or ammonium formate /formic acid.

Compounds of formula IV are known compounds, and can be produced by methods known in the art such as the procedure disclosed in US 5606064, example 1.

Suitable solvents for hyrogenation of the compounds of formula II or IV are the customary inert solvents that do not change under the reaction conditions. Examples of such solvents include ethers, such as dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran; alcohols such as methanol, ethanol, propanol, isopropanol and butanol; chlorinated hydrocarbons such as dichloromethane, tetrachloromethane and dichloroethylene; esters such as ethyl acetate and isopropyl acetate; ketones such as acetone and MIBK (methylisobutylketone); hydrocarbons such as hexane, toluene, and xylene; water; dimethylformamide; dimethyl sulphoxide; N-methylpyrrolidone; and mixtures thereof.

The base used for preparing a benzyl-piperidylmethyl-indanones of formula I, may be an amine, an inorganic base or ammonia. Examples of amines include triethylamine, N-methyl morpholine, N,N-dimethyl benzyl amine, pyridine, picoline, and lutidine.

The inorganic base used for preparing a benzyl-piperidylmethyl-indanones of formula I, may be an alkali metal carbonate, bicarbonate or hydroxide. Examples of alkali metal carbonates include lithium carbonate, potassium carbonate and sodium carbonate. Examples of alkali metal bicarbonates include potassium bicarbonate and sodium bicarbonate. Examples of alkali metal hydroxides include potassium hydroxide and sodium hydroxide.

Phase transfer catalysts used for preparing a benzyl-piperidylmethyl-indanones of formula I, are not limited though, they are quaternary ammonium salts, or quaternary phosphonium salts generally. Examples of quaternary ammonium salts include tetramethylammonium iodide, tetrabutylammonium iodide, benzyltributylammonium bromide, 1-methylpiridinium iodide, teramethyl-2-butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide, and t-butylethyldimethylammonium bromide. Examples of quaternary phosphonium salts include tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutylphosphonium bromide, benzyltriphenylphosphonium bromide, and tetraphenylphosphonium chloride.

Compounds of formula II can be produced by methods known in the art such as the procedures disclosed in US 6413986, WO 97/22584, J. Med.Chem. 1995, 38 (24), 4821-4829, or obtained by the reduction of compounds of formula III.

Solvents in the benzylation reactions are not limited either, and customary organic solvents, which do not change in the reaction may be used. Examples of such solvents include water; ethers such as diethyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran; chlorinated hydrocarbons such as dichloromethane, and

dichloroethylene; esters such as ethyl acetate and isopropyl acetate; ketones such as acetone and MIBK (methylisobutylketone); alcohols such as methanol, ethanol, propanol and isopropanol; acetonitrile; dimethylformamide; dimethyl sulphoxide; 1,2-dimethoxyethane; N-methylpyrrolidone; sulpholane; and mixtures thereof.

The temperature at which the benzylation reaction may be carried out is not critical. For example the reaction may be carried out at a temperature range from –20°C to 120°C, or at a temperature range from 0°C to 40°C. In one particular example it may be carried out at a temperature range from 10°C to 35°C.

In the following section preferred embodiments are described by way of examples to illustrate the process. However, these are not intended in any way to limit the scope of the claims. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Preparation 1

Preparation of 5,6-dimethoxy-2-(pyridine-4-yl) methylene-indan-1-one

A mixture of 5,6-dimethoxy-indan-1-one (100g), pyridine-4-carboxaldehyde (67gm, p-toluene sulfonic acid (118g) in toluene (1200ml) was refluxed azeotropically for 6 hours. After cooling the reaction mixture to room temperature followed by filtration, the wet solid was stirred with 10% aqueous sodium carbonate solution. Filtration of the solid followed by washing with acetone and then drying afforded the title compound (130g).
HPLC Purity: 99.5%

EXAMPLE 1

Preparation of 5,6-dimethoxy-2-(4-pyridyl)methyl-indan-1-one.

5,6-dimethoxy-2-(pyridine-4-yl) methylene-indan-1-one (100g from preparation 1) was hydrogenated using 10% Palladium/carbon (10g, 50% moisture) in a mixture of methanol (1500ml) and methylene chloride (1000ml) at atomospheric pressure (buggling with H2 gas) for 5 hours. Filtration of the reaction mixture followed by concentration of the solution afforded the title compound (92 g).
HPLC Purity : 99.8%.

EXAMPLE 2

Prepration of 2,3-dihydro-5,6-dimethoxy-2-(4-piperidinyl)methyl-indan-1-one, hydrochloride

A mixture of 5,6-dimethoxy-2-(4-pyridyl)methyl-indan-1-one (25g from example 1), methanol (125ml), water (125ml), Conc. Hydrochloric acid(12.5g) and Platinum dioxide (2.5g) was hydrogenated at 15 to 20 psi hydrogen pressure for 6 hours. Filtration of the reaction mixture followed by concentration afforded a residue which was crystallized from methanol to get title compound (24g).
HPLC Purity: 99.4%.

EXAMPLE 3

Preparation of 1-benzyl-4-((5,6-dimethoxy-l-indanone)-2-yl)methylpiperidine, hydrochloride (donepezil hydrochloride)

To a stirred mixture of 2,3-dihydro-5,6-dimethoxy-2-(4-piperidinyl)methyl-indan-1-one, hydrochloride (10g from example 2), tetrabutyl ammonium bromide (1g), potassium carbonate (9g) in a mixture of water (40ml) and methylene chloride (50ml) was added

benzyl bromide (5.3g) at 20-25°C in over 30 minutes. After addition, stirred the reaction mixture at the same temperature for 30 minutes. The organic layer was separated and stirred with a mixture of water (20ml) and conc. hydrochloric acid (6.4g) at 20-25°C for 15 minutes. The organic layer was separated and concentrated. The residue was dissolved in water (100ml) and extracted with ethyl acetate (50ml). The organic layer was discarded and pH of the aqueous layer was adjusted to 9.5 with aqueous ammonia solution (3.5ml). The aqueous solution was then extracted with ethyl acetate (50ml). The ethyl acetate extract was washed with water. The organic layer was concentrated and the residue was dissolved in methanol (50ml). To the solution was added conc. hydrochloric acid (4.8g) diluted with methanol (10ml). Diisopropylether (120ml) was then added to the solution at 25°C. Solid that separated out on stirring at 5 to 10°C was filtered and dried to get crystals of donepezil HCl (10g).

HPLC Purity : 99.95%.

WE CLAIM:

1. A process for preparing a 2-(4-piperidinyl) methyl-1-indanone of formula II, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are identical or different, and represent hydrogen, straight or branched -chain alkyl, alkoxy, alkoxycarbonyl, alkyl- or dialkyl-aminocarbonyloxy, trifluoromethyl, or halogen, comprising reducing a 2-(4-pyridyl) methyl-1-indanone of the formula III, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above.
2. The process according to claim 1 for the preparation of a compound of formula II, wherein R^1 and R^4 represent hydrogen and R^2 and R^3 represent methoxy.
3. The process according to claim 1, wherein the reduction comprises hydrogenation in the presence of a catalyst.
4. The process according to claim 3, wherein the catalyst is selected from the group consisting of platinum oxide, ruthenium oxide, and rhodium/carbon.
5. The process according to claim 3, wherein the hyrogenation is carried out at a pressure of from 1 to 2 atmospheres using hydrogen gas.
6. The process according to claim 3, wherein the hyrogenation is carried out at a temperature of from about 10°C to about 35°C.
7. The process according to claim 3, wherein the hyrogenation is carried out in a solvent selected from the group consisting of ethers, alcohols, chlorinated hydrocarbons, esters, ketones, hydrocarbons, water and mixtures thereof.
8. The process according to claim 7, wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol and butanol.
9. The process according to claim 1, wherein the 2-(4-pyridyl) methyl-1-indanone of formula III, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above, is prepared by selectively reducing 2-(4-pyridyl) methylene-1-indanone of formula IV, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above.

10. The process according to claim 9 for the preparation of a compound of formula III, wherein R^1 and R^4 represent hydrogen and R^2 and R^3 represent methoxy.
11. The process according to claim 9, wherein the reduction comprises hydrogenation in the presence of a catalyst.
12. The process according to claim 9, wherein the catalyst is selected from the group consisting of palladium/carbon, platinum/carbon and Raney nickel.
13. The process according to claim 9, wherein the hyrogenation is carried out at a temperature of from about 10°C to about 35°C.
14. The process according to claim 9, wherein the hyrogenation is carried out in a solvent selected from the group consisting of ethers, alcohols, chlorinated hydrocarbons, esters, ketones, hydrocarbons, water, and mixtures thereof.
15. The process according to claim 14, wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol, isopropanol and butanol.
16. The process according to claim 14, wherein the chlorinated hydrocarbon is selected from the group consisting of dichloromethane, tetrachloromethane and dichloroethylene.
17. The process according to claim 1, characterized in that the 2-(4-piperidinyl) methyl-1-indanone of formula II, wherein R^1, R^2, R^3, and R^4 are as defined above is reacted with a benzyl derivative of formula V, wherein X is a leaving group to obtain a benzyl-piperidylmethyl-indanones of formula I, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are as defined above.
18. The process according to claim 18, wherein the base is selected from the group consisting of amine, an inorganic base and ammonia.
19. The process according to claim 18, wherein the reaction is performed in the presence of an inorganic base and a phase transfer catalyst.

20. A process for preparing a benzyl-piperidylmethyl-indanones of formula I, as shown in the accompanied drawings, or a salt thereof, wherein R^1, R^2, R^3, and R^4 are identical or different, and represent hydrogen, straight or branched -chain alkyl, alkoxy, alkoxycarbonyl, alkyl- or dialkyl-aminocarbonyloxy, trifluoromethyl, or halogen, comprising reacting a 2-(4-piperidinyl) methyl-1-indanone of the formula II, as shown in the accompanied drawings, wherein R^1, R^2, R^3, and R^4 are as defined above, with a benzyl halide in the presence of an inorganic base and a phase transfer catalyst.

21. The process according to claim 17, or 20 for the preparation of a compound of formula I, wherein R^1 and R^4 represent hydrogen and R^2 and R^3 represent methoxy.

22. The process according to claim 17, or 20 wherein the leaving group X in the benzyl derivative of formula V is chloride, bromide, iodide, tosylate, or sulphate.

23. The process according to claim 19, or 20 wherein the inorganic base is an alkali metal carbonate.

24. The process according to claim 23, wherein alkali metal carbonate is selected from the group consisting of lithium carbonate, potassium carbonate and sodium carbonate.

25. The process according to claim 19, or 20 wherein the phase transfer catalyst is selected from the group consisting of quaternary ammonium salt, or quaternary phosphonium salt.

26. The process according to claim 22, wherein the quaternary ammonium salt is selected from the group consisting of tetramethylammonium iodide, tetrabutylammonium iodide, teramethyl-2-butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide, and t-butylethyldimethylammonium bromide.

27. The process according to claim 17, or 20 wherein the reaction is carried out at a temperature of from about 0°C to 40°C.

28. The process according to claim 17, or 20, wherein the reaction is carried out in a solvent selected from the group consisting of ethers, alcohols, chlorinated hydrocarbons, esters, ketones, water, and mixtures thereof.

29. The process according to claim 17, or 20, wherein the chlorinated hydrocarbon is selected from the group consisting of dichloromethane, tetrachloromethane and dichloroethylene.

30. The process for preparing benzyl-piperidylmethyl-indanones of formula I, as herein described and illustrated by the examples herein. herein

Dated this **21ST** day of **March, 2003.**

For RANBAXY LABORATORIES LIMITED

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

Processes for the preparation of piperidylmethyl-indanones, which are useful intermediates for the preparation of benzyl-piperidylmethyl-indanones, are provided. Further, processes for the preparation of benzyl-piperidylmethyl-indanones, which are active compounds for the treatment of CNS disorders, are provided.

Ranbaxy Laboratories Limited

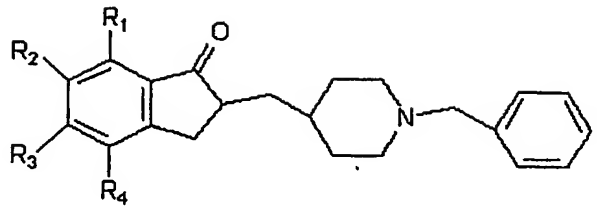
Application No.

No. of sheets = 04

Sheet 01 of 04

0352-DEL-03

21 MAR 2003



Formula I

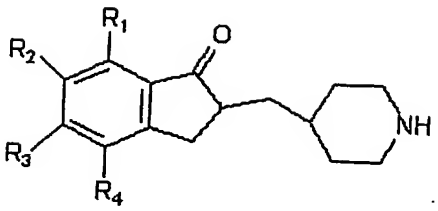
ORIGINAL

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited
Application No.

No. of sheets = 04
Sheet 02 of 04



Formula II

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

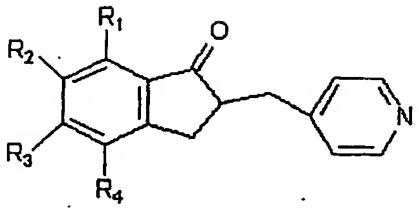
Application No.

No. of sheets = 04

Sheet 03 of 04

0752-DEL-03

21 MAR 2003



Formula III

ORIGINAL

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

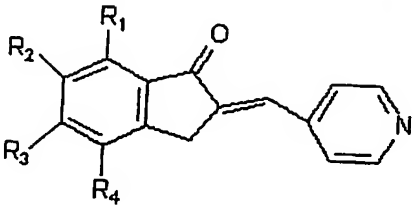
Application No.

No. of sheets = 04

Sheet 04 of 04

0752-DEL-03

21 MAR 2003



Formula IV

ORIGINAL

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

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